



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Neil H. Bander

Art Unit : 1642

Serial No. : 09/929,546

Examiner : Gary Nickol

Filed : August 13, 2001

Title : TREATMENT AND DIAGNOSIS OF CANCER

Commissioner for Patents

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DECLARATION OF JEFFREY ROSS, M.D. UNDER 37 CFR §1.132

I, Jeffrey Ross, M.D., pursuant to 37 C.F.R. § 1.132, declare the following:

1. My educational and professional experience and qualifications are presented in the attached Curriculum Vitae (Appendix H).
2. I am currently employed by Millennium Pharmaceuticals, Inc. as a consultant on the anti-prostate specific membrane antigen (PSMA) antibody project.
3. I have reviewed the Office Action mailed August 26, 2003 regarding the above-referenced application and understand that the Examiner has rejected the claims asserting that "with regards to the treatment of subjects with cancer comprising the presently claimed antibodies, the specification does not provide sufficient guidance or objective evidence that such methods would predictably and effectively function to treat a subject as claimed."
4. Throughout the application, it has been demonstrated that PSMA is highly expressed by vascular endothelial cells of numerous non-prostate malignancies but not in the vascular endothelial cells of normal and benign tissue. For example, the results of Example 13 of the application show that antibodies against the extracellular domain of PSMA bind the neovasculature of renal carcinomas, urothelial carcinomas, colon carcinomas, rectal carcinomas, lung carcinomas, breast cancer and metastatic adenocarcinoma of the liver. Additional studies performed by myself and others have demonstrated that in addition to the malignancies listed above, PSMA is expressed in the neovasculature of ovarian cancer, neoendocrine cancers, glioblastomas, melanomas, pancreatic cancers, soft tissue sarcoma and kidney cancers. (See Exhibit D, Abstract from the 94th Mtg. of the American Association for Cancer Research, July 11-14 2003;

Mtg. of the United States and Canadian Academy of Pathology (USCAP) Research, January 2004; Modern Pathology Volume 17(1)). Thus, the specificity of PSMA expression in the vascular endothelial cells of various non-prostate cancers, but not in vasculature of normal or benign tissue has been demonstrated. In addition, it has been shown that antibodies against PSMA target PSMA expressed in the vasculature of these malignant tissues.

5. Human clinical trials, using methods of the invention, have begun. These Phase I dose escalation trials, demonstrate *in vivo* targeting of vascular endothelial cells of various solid tumors with an antibody that binds the extracellular domain of PSMA. ¹¹¹Indium-labeled deJ591 (an antibody against the extracellular domain of PSMA) has been administered to nine patients having refractory solid tumor malignancies known to express PSMA on the neovasculature. These include patients having renal, bladder and colon cancer. Indium scanning showed localization of deJ591 to tumor sites in a majority of these patients. In addition, at least three of these patients demonstrated an improvement in a symptom of their cancer. (See Milowsky et al., 2002 American Society for Clinical Oncology Mtg; abstract #29, attached herewith as Exhibit F). Additional studies have also demonstrated *in vivo* targeting of the neovasculature of melanoma and lung metastases in human subjects. Indium scans of some of these results are provided herewith as Exhibits A-C. Exhibit A shows a CT scan and an indium scan of a patient having renal cancer and receiving ¹¹¹In labeled J591. As can be seen in Exhibit A, both CT and indium scans demonstrate targeting of J591 to a lung metastases in the subject. Exhibit B demonstrates *in vivo* targeting of ¹¹¹In labeled J591 to the neovasculature of melanoma in a human subject. Exhibit C demonstrates *in vivo* targeting of ¹¹¹In labeled J591 to the neovasculature of a colon cancer in a human subject. In my opinion, the data discussed in this Declaration show that the specification provides sufficient guidance to allow one of ordinary skill in the art to practice the claimed invention without undue experimentation.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the



Attorney's Docket No.: 10448-184008 / MPI1996-037P2RCP1DV1ACN1A; CRF D-1912L

like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 2/24/04


Jeffery Ross, M.D.

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